REMARKS

Claims 13-19 are pending in the application following entry of the amendments. Claims 18 and 19 have been added. Support is found in the original claims and in the specification on page 4, lines 3-6. Claims 13 and 16 have been amended to ascribe a function for the oligopeptides, as consistent with the specification (see, *e.g.*, page 3, lines 17-19). Minor amendments have been made to claim formalities for Claims 14-16. No new matter is entered by way of the amendments.

Applicant respectfully requests entry of the amendments and reconsideration of the final rejections in view of the following comments with respect to the pending claims.

Rejections Under 35 U.S.C. § 112, second paragraph: indefiniteness

Claims 13 and 16 stand rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Applicant respectfully traverses the rejection.

Examination of a claim for definiteness must take into consideration (a) content of the application disclosure, (b) teachings of the prior art, and (c) claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See M.P.E.P. § 2173.02. The legal standard is whether a "claim reasonably apprises those skilled in the art of its scope." See In re Wamerdam, 31 USPQ2d 1754, 1759 (Fed. Cir. 1994). The Federal Circuit emphasizes

> If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2. . . . . We have not insisted that the claims be plain on their face in order to avoid condemnation for indefiniteness; rather what we have asked is that the claims be amenable to construction, however difficult that task may be.

See Exxon Research and Engineering Co. v. United States, 60 USPQ2d 1272, 1276 (Fed. Cir. 2001).

Applicant submits that Claim 13 is amenable to a reasonably clear construction, and defines the claimed subject matter with the requisite particularity and distinctness to satisfy 35 U.S.C. § 112, second paragraph. Specifically, the specification describes the claimed peptide with clear reference to sequences of the HLA-B α_1 domain used to extend the triad YYW:

> [C]ytomodulating peptides are provided having the tripeptide tyrosine-tyrosine-tryptophan, where the N terminus is *extended* by at least 3 amino acids, of the human Class I HLA-B α1 domain . . .

(specification on page 3, lines 5-8). Further, the specification beginning on page 3, line 34 provides:

> The C terminus of the triad may also be *extended*, usually by not more than 5 amino acids, more usually by not more than 3 amino acids, frequently not more than 1 amino acid.

These features are reiterated in Claim 13 by express reference to sequences of the HLA-B α_1 domain, where the claimed oligopeptides have the triad YYW at amino acid positions corresponding to residues 84-86 of the HLA-α_1 domain. As discussed in Applicant's previous response, the boundaries of the HLA-B α_1 domain have been well delineated, and its sequence is well known to the skilled artisan.

Further, the claim language, as supported by the disclosure, specifies "a *contiguous* sequence of the HLA-B α_1 domain." A person of ordinary skill in the art would have no difficulty construing the claimed oligopeptide as having an amino acid sequence that extends *contiguously* from amino acid positions 84-86 of the HLA-B α_1 domain, as modified with respect to residues at the specified amino acid positions. Thus, the scope of Claim 13 is sufficiently clear to reasonably apprise those of ordinary skill in the art infringing or non-infringing embodiments.

Nothwithstanding the amenability of the claim to a clear construction, Applicant, in an effort to advance prosecution of this case and without agreeing with the Examiner's position, has amended Claim 13 to restate what is inherent in original Claim 13 and in terms consistent with the specification.

Claim 16 is rejected for indefiniteness for alleged inconsistency between the scope Claim 15 and the oliogopeptide of Claim 16. Applicant respectfully traverses the rejection.

Claim 16 recites an oligopeptide of *at least* 10 amino acids. The oligopeptide of Claim 15 is not 10 amino acids but is *at least* 10 amino acids in length. Thus, the oligopeptide of Claim 16 is within the literal scope of "*at least* 10 amino acids." The Examiner's rejection in this case is without basis. However, in an effort to advance prosecution of this case and in light of the Applicant's comments to the rejection, Claim 16 has been amended to delete the allegedly objectionable phrase.

Rejections Under 35 U.S.C. § 112, first paragraph: enablement

Claims 13, 14, 16, and 17 stand rejected under 35 U.S.C. § 112, second paragraph for alleged lack of enablement. Applicant respectfully traverses the rejection.

Applicant invites the Examiner to review the specification on page 22, lines 51-57, which describes biological activities of peptide 15 (SEQ ID NO17), peptide 16 (SEQ ID NO:18), peptide 17 (SEQ ID NO:19) and peptide 19 (SEQ ID NO:21), all of which contain the triad YYW and are within the scope of the claimed compounds. Peptide 15 (SEQ ID NO17) displayed the highest CTL inhibitory activity, while peptide 16 (SEQ ID NO:18), and peptide 19 (SEQ ID NO:21) were found to be "substantially greater" than control in inhibiting CTL activity. The disclosure further states that peptides 15, 16, and 17 inhibited stimulation of lymphocytes by anti-CD3 antibodies. It is notable that although these olipepeptides have significant deletions and/or additions to the carboxy or amino terminus surrounding the sequence YYW, they maintained CTL inhibitory activity. This retention of function is clear evidence that the claimed oligopeptides having additional sequences added to the amino or carboxy terminus can produce oligopeptides displaying the requisite biological activity. Thus, the teachings of the specification are reasonably correlated with the oligopeptides *comprising* the recited sequences.

The Examiner advances a number of reasons for judging the claims nonenabled. One rationale is that the specification and the claims purportedly do not define the structural and functional characteristics of the core structure in the compounds of SEQ ID NOs 3-56 essential to maintain biological activity. A person of ordinary skill in the art, however, would clearly recognize SEQ ID NOs 17-21 as being encompassed by the claims while the other sequences, which lack the triad YYW, are excluded. The exemplary oligopeptides are literally *at least* 6 amino acids and comprise a contiguous sequence of the HLA-B α_1 domain, where the oligopeptides include the residues corresponding to amino acid positions 84 to 86 of the HLA-B α_1 domain except as modified at the enumerated residue positions. Further, the claims and specification recite a specific biological activity associated with the compounds. Therefore, the plain meaning of the claims is unambiguous in denoting the essential sequences of the oligopeptides and its related functional property.

In further asserting the rejection, the Examiner points to page 10, lines 10-20 of the specification as purportedly suggesting that only certain amino acids at specific positions display lymphocyte modulatory activity. The Examiner use of the passage, however, is puzzling since the paragraph refers to generation of mutational variants where amino acid changes are made "except as specifically indicated" (*i.e.*, invariant residues YYW). The passage does provide a generalized discussion about changes to amino acids involved in protein interactions, but a person skilled in the art would not translate this description into an explicit reference that only particular amino acid residues can be used at certain specified amino acid positions to retain biological activity. Contrary to the Examiner's inference, the passage provides an enabling disclosure for identifying variants with the requisite structure and activity.

Another passage cited in the Office Action concerns page 22, lines 5-30 of the specification, which is offered to support the assertion that only a few of the claimed sequences display the requisite functional activity, with peptide E being cited as a specific example of a peptide encompassed by the claims but devoid of biological activity. However, peptide E (SEQ ID NO:45) is not within the scope of the claimed subject matter because it does not contain the triad YYW in the specified residue position.

Although the Examiner's proffers the reference Ngo et al., *Protein Folding Problem and Tertiary Structure Prediction*, Birkhauser, ed., pp 433 and 492-495, Boston, MA (1994) to support the rejection, this reference is not applicable to the present claims for several reasons. First, the Ngo reference is directed to difficulties in identifying a mathematical algorithm for predicting protein folding, but does not address the issue of the unpredictability of biological activity in relation to changes in the amino acid sequence of a protein. Lack of a defined algorithm for predicting protein folding in no way precludes an understanding of the structure-function relationship, a position clearly supported by the Bowie, J.U., et al., *Science* 247:1306-1310 (1990) reference used by the Examiner in the prior Office Action. The Bowie reference provides a clear and cogent step-by-step method for defining the structure-function relationship through use of substitution mutations, which generates information as to which residues can be altered and the permissible variations for each residue position. As pointed out by the authors, this approach does not require knowledge of any protein folding algorithm and is particularly useful in situations where sequences of related peptides are not available (see page 1310, left column, first paragraph).

Second, unpredictability of function in relation to changes in oligopeptide sequence depends on the specific sequence. A general extrapolation of unpredictability to all oligopeptides cannot be made, as underscored by the stability of signal sequences to variations around the core sequence (see Applicant's response of November 24, 2003). Further, the Bowie reference is illustrative of how the core sequence of a biologically active peptide can be predictably changed while maintaining activity. Bowie shows that the person of ordinary skill in the art uses routine experimentation to identify sequence elements that can be altered to generate biologically active compounds comprising a defined oligopeptide sequence.

In summary, Applicant has disclosed HLA-B α_1 domain derived oligopeptides containing the triad YYW that maintained biological activity despite significant variations in the amino or carboxy terminal sequences. Thus, there exists a reasonable correlation between the teachings of the specification and the scope of the claimed oligopeptides comprising the recited sequences. Based on this disclosure, a person skilled in the art could use standard experimental techniques to determine which other embodiments *comprising* the recited oligopeptides that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort that is normally required. See M.P.E.P. § 2164.08(b). In such cases, disclosure is not required of a test with every species covered by a claim. *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976).

Accordingly, withdrawal of the rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejections Under 35 U.S.C. § 112, first paragraph: written description

Claims 13, 14, 16, 17 stand rejected under 35 U.S.C. 112, second paragraph for alleged insufficient written description. Applicant respectfully traverses the rejection.

The standard for written description imposed by the Examiner in this case is based on the holding in University of California v. Eli Lilly, 43 USPQ2d 1398 (Fed. Cir. 1997), as supported by earlier case of Fiers v. Revel, 25 USPQ2d 1601 (CAFC 1993). The Office Action elaborates the following standard for written description:

> Adequate written description requires more than a mere statement that is part of the invention. The *sequences themselves are required. . .* A description of a genus of protein sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or

> of a recitation of structural features common to the genus, which feature constitute a substantial portion of the genus.

(emphasis added). The Federal Circuit, however, has modified the effect of University of California v. Eli Lilly in subsequent decisions. See Enzo Biochem Inc. v. Gen-Probe Inc., 63 USPQ2d 160 (Fed. Cir. 2002); see also Amgen Inc. v. Hoechst Marion Rousel Inc., 65 USPQ2d 1385 (Fed. Cir. 2003). Rather than a strict requirement for a "precise definition, such as by structure, formula, chemical name, or physical properties," the court held that a *functional* characteristic coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed may satisfy the written description requirement. See Enzo Biochem Inc. v. Gen-Probe Inc. at 1613. Thus, the broad sweep of University of California v. Eli Lilly in the manner applied to the pending claims is not supported by the decisions of the Federal Circuit.

Further in Enzo Biochem Inc., the court viewed with approval the Synopsis of Written Description Guidelines issued by the USPTO. See 63 USPQ2d at 1613. Applicant invites the Examiner to review Example 14 of the USPTO guidelines. The hypothetical claim is directed to variants of a protein sequence, where the protein is novel, unobvious, displays an identifiable functional characteristic, and is at least 95% identical to the recited sequence. Only a single sequence is disclosed. As the transitional language of the claim is open ended (*e.g.*, comprises), the guideline describes the protein as encompassing proteins "larger" than the described sequence, in addition to variants with substitutions, deletions, and insertions. The specification does not disclose exemplary variants. Under this factual situation, the USPTO concludes the claim satisfies the written description requirement.

In the instant case, Claim 13 specifies oligopeptides based on the HLA-B α_1 domain. The claimed oligopeptides include the triad YYW corresponding to positions 84-86 of the HLA-B α_1 domain and is described as displaying a specific biological activity. Primary structures of the HLA-B-α_1 domain are well known to the person of ordinary skill in the art. Further, the term HLA-B α_1 itself denotes an identifiable secondary structure as evidenced by the study of Bjorkman, P.J. et al., "The foreign antigen binding site and T cell recognition regions of class I histocompatability antigens," *Nature* 329:512-518 (1987), submitted in Applicant's response of November 20, 2003). The claim encompasses different types of variants and includes embodiments larger than the specified oligopeptide. Thus, it is readily apparent that the form and content of Claim 13 is comparable to the illustrative claim

described by the Patent Office as satisfying the written description requirement. Further, whereas only a single species is disclosed for the hypothetical example in the guidelines, numerous sequences of HLA α_1 domain, including natural variants, were known in the art.

The Federal Circuit has restricted the application of University of California v. Eli Lilly to the particular facts of the case, and Federal Circuit precedent is in conflict with the written description standard applied in this case by the Examiner. It is submitted that application of the USPTO guidelines, as illustrated by the court in Enzo Biochem Inc., will show that Claim 13, and likewise Claims 14, 16, and 17, satisfy the written description requirement under § 112, first paragraph.

CONCLUSION

Applicant submits that the pending claims satisfy all the requirements for patentability and are in condition for allowance. If the Examiner believes there are unresolved issues that are better addressed by a telephone interview, the Examiner is invited to direct any calls in connection with this application to the undersigned attorney at (415) 781-1989.

No fees are believed due with this submission. The Commissioner, however, is authorized to charge any required fees, or credit any overpayment to Dorsey & Whitney LLP Deposit Account No. 50-2319 (Order No. A-61008 (465840-00078)/TAL/CYO).

Respectfully submitted,

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